

# Sequential Therapy with Induction Chemotherapy Followed by Concurrent Chemoradiation in Locally Advanced Squamous Cell Carcinomas of the Head and Neck

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## ABSTRACT

**Introduction:** Induction chemotherapy in locally advanced head and neck cancers prior to local therapy has been demonstrated to be non-inferior to concurrent chemoradiation in terms of overall survival (OS). Despite possible lack of survival advantage, downsizing of tumours, allowing organ preservation along with the possible benefit of eradication of micrometastases earlier in the course of therapy makes this a desirable approach for many heads and neck oncologists worldwide. Study aimed to assess the immediate locoregional response rates and to assess the toxicity profile of sequential therapy with three cycles of induction PFT followed by Concurrent Chemo-Radiation with weekly Cisplatin in Locally Advanced Head and Neck Cancers.

**Material and methods:** 30 consecutive patients with locally advanced head and neck cancers attending the OPD at our institute were included in the study. All patients were treated with 3 cycles of Induction chemotherapy with PFT regimen (Paclitaxel 175mg/m<sup>2</sup> Day1, Cisplatin 100 mg/m<sup>2</sup> split to (Day 1-3), 5-FU 750 mg/m<sup>2</sup> Day 1 to 3) every 21 days. The patients were then taken up for concurrent chemoradiation (66 Gy RT along with weekly Cisplatin 40mg/sq.m.). The immediate locoregional response rates were assessed by clinical and radiological imaging. The toxicity profile of the treatment was assessed with RTOG acute morbidity scoring criteria and CTCAE Version 4.

**Results:** 30 patients (3 female) were recruited for the study. Among them 3 were laryngeal cancer patients and the hypopharyngeal, oropharyngeal and the oral cavity cancers were 9 each. 63% of them had complete response and 30% had partial response. The sub-sites of the hypopharynx and the oropharynx had the best outcomes from this treatment protocol. 2 patients did not complete the planned treatment. 11 patients had grade 3 leukopenia and 2 patients had grade 4/ febrile neutropenia. There was no grade 3 thrombocytopenia in the study group.

**Conclusion:** Sequential therapy with three cycles of induction PFT followed by concurrent chemoradiation is a feasible alternative for moderately advanced and very advanced head and neck cancer. Patient selection and supportive care during treatment are very important for successful outcome.

**Keywords:** Sequential Therapy, Induction Chemotherapy, Concurrent Chemoradiation, Advanced Squamous Cell Carcinomas, Head and Neck

chemoradiation has been investigated as a method of further improving outcomes among these patients, but its application remains controversial. Several randomized clinical trials have performed a comparison of induction chemotherapy followed by Concurrent chemoradiation to Concurrent chemoradiation alone in locally advanced head and neck squamous cell carcinoma; the majority of these studies have not demonstrated a survival benefit with the addition of induction chemotherapy.<sup>4-8</sup> Previous studies addressing this question have included a heterogeneous population of all head and neck subsites with both p16-positive and p16-negative disease and varying extent of nodal disease burden. In contrast to the patterns of failure seen in p16-negative disease, distant failure constitutes a considerable portion of treatment failures in p16- positive disease.<sup>9,10</sup> induction chemotherapy has the potential to improve distant control by eliminating micrometastatic disease; however, this benefit is only likely to be seen in those patients who are at the highest risk for distant failure.

Study aimed to assess the immediate locoregional response rates and to assess the toxicity profile of sequential therapy with three cycles of induction PFT followed by Concurrent Chemo-Radiation with weekly Cisplatin in Locally Advanced Head and Neck Cancers.

## MATERIAL AND METHODS

The present study was a Single Arm Prospective Study of previously untreated patients receiving sequential therapy for locally advanced head and neck cancer. The study got approval from the Ethics Committee of the institution prior to opening for accrual and all patients signed an informed consent form in Tamil prior to participating in the study.

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## INTRODUCTION

Concurrent chemoradiation is the standard of care for locally advanced head and neck squamous cell carcinoma.<sup>1-3</sup> The addition of induction chemotherapy to Concurrent

30 consecutive patients of locally advanced head and neck cancers attending the Out-Patient Department at our Institute who met the inclusion criteria were enrolled in the study. Eligible patients had to have histologically or cytologically proven squamous cell carcinoma in the head and neck region in the locally advanced stage by TNM staging. They had to be eligible for curative treatment on the basis of the extent of their disease, medical comorbidities, distant metastasis and/or combination of these factors.

#### Inclusion Criteria

- Biopsy proved squamous cell carcinoma of the head and neck.
- Primary tumor sites are eligible: oral cavity, oropharynx, hypopharynx, larynx.
- Age >18 years to < 70 years.
- Stage III or IV disease without evidence of distant metastases.
- ECOG Performance Status 0 – 2.

#### Exclusion Criteria

- Patient is not consenting to chemotherapy at any point in the treatment.
- Previously received treatment for any other malignancy.
- Tumors of the nasal cavity, paranasal sinuses and nasopharynx.
- Non-Squamous Histopathology.
- Inadequate hepatic and renal functions.

#### Pre-Treatment Work Up

1. Elucidate the history of the symptoms.
2. Visual examination and palpation of the oral cavity and proximal oropharynx.
3. Neck examination for regional lymph nodes involvement.
4. Thorough clinical examination of the entire upper aerodigestive tract to rule out a second primary. IDL and VDL scopy, direct nasal examination, anterior and posterior rhinoscopy.
5. Biopsy from tumor or FNAC from neck node.
6. Complete blood count, renal and liver function tests before every cycle of induction chemotherapy.
7. CT scan Neck (From Base of Skull to Root of Neck) – Plain and Contrast before the start of treatment and after completion of induction chemotherapy and at first follow up.
8. Chest X-Ray – PA view.
9. X-Ray Mandible to rule out cortical bone involvement.
10. Weekly blood counts and renal function tests during radiotherapy.
11. Cardiology fitness for chemotherapy.
12. Nasogastric intubation as required before starting treatment.
13. Dental prophylaxis by extraction, filling and scaling.

All patients were treated with three cycles of induction chemotherapy given every 21 days over a period of three days on an inpatient basis. All the patients were assessed on Day 8 -10 of every cycle with complete blood count for myelosuppression. Patients with suppression were kept under close observation. No intervention was allowed. If the

patient had febrile neutropenia/Grade 4 neutropenia, they were treated with G-CSF 300mcg s.c. on days 1-3. All other grades of myelosuppression were kept under observation and assessed before the start of the next chemotherapy. If myelosuppression still persisted they were treated with G-CSF with the above-mentioned schedule. All patients who needed secondary prophylaxis in previous cycles as per the above mentioned protocol were given primary prophylaxis with GCSF in the subsequent cycles of chemotherapy during Days 8-10 of the cycle.

The patients with a response to chemotherapy were then taken up for Radical Concurrent Chemo Radiation.

#### Radiotherapy Technique

The radiation was delivered in conventional fractionation with a Theratron Phoenix Tele Cobalt – 60 machines. The radiation was delivered on an out-patient basis for local patients or on an in-patient basis for patients from other localities. All the patients were delivered the weekly chemotherapy on an in-patient basis every week.

**Dose per fraction:** 2 Gy per fraction over 5 days a week.

**Total dose:** 66Gy to the gross tumor and positive nodes and 50 Gy to the elective nodes.

Radiotherapy was delivered by opposing lateral fields in a Theratron Phoenix Tele-Cobalt machine in 200cGy per fraction for 5 days a week. Patients are given a break on Saturday and Sunday. Appropriate shielding of the spinal cord was done after the tolerance dose of the spinal cord was reached at 40 Gy. In view of the intense regimen of induction phase chemotherapy which is being followed up with concurrent chemoradiation, all patients were started on prophylactic measures to prevent the development of mucositis and infection during radiotherapy.

**Weekly Chemotherapy:** The patients also received concurrent chemotherapy of weekly Cisplatin at a dose of 40mg/m<sup>2</sup> after assessing the renal parameters and the hemoglobin levels. The entire treatment schedule was to be completed in 6.3 weeks. Patients with progressive disease after induction chemotherapy were taken up for palliative chemotherapy/radiotherapy.

Toxicity in the present study was graded using Common Toxicity Criteria Version 4 and RTOG Acute Radiation Morbidity Scoring Criteria.

Tumor response will be evaluated 4-6 weeks after the end of course with CT Neck from the base of the skull to root of the neck and clinical examination. The criteria used were RECIST 1.1 Criteria.

Patients were assessed for disease status 1 month after the end of treatment and every month thereafter. During follow up, a thorough history, physical examination and complete clinical examination were done.

#### RESULTS

The present study enrolled a total of 30 patients with histologically proven locally advanced squamous cell carcinoma of the head and neck region. Among the 30

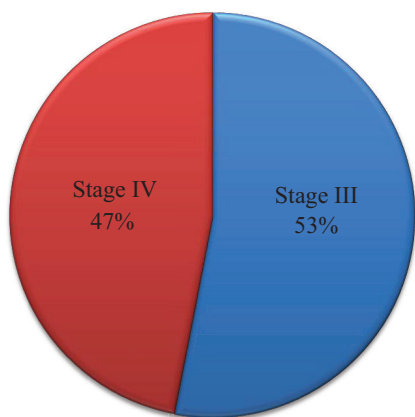


Figure-1: Stage Grouping

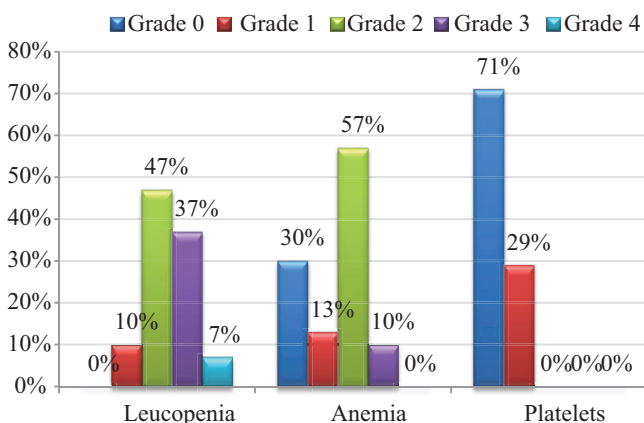


Figure-2: Hematological toxicities in induction chemotherapy

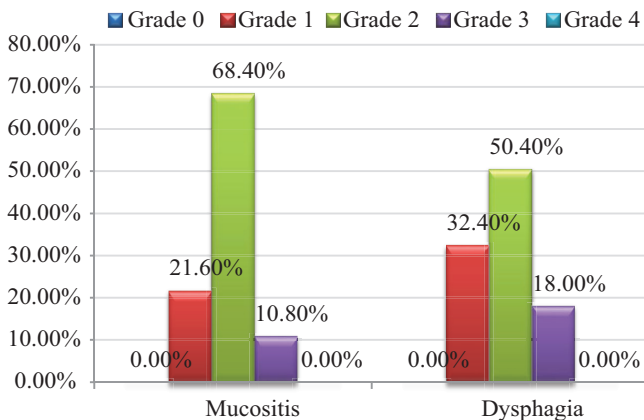


Figure-3: Toxicity during Radiotherapy

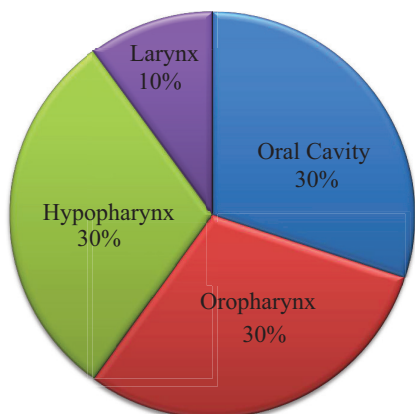


Figure-4: Site Distribution

Factors	Complete response	Partial response
T1	2	0
T2	7	0
T3	4	1
T4	6	8
N2	12	4
N3	5	2
Oral Cavity	4	5
Oropharynx	6	1
Hypopharynx	8	1
Larynx	1	2
Stage III	13	3
Stage IV	6	6
Well Diff	0	4
Mod. Diff	12	5
Mod. Diff	6	5
Delay in RT	4	5

**Table-1: Factors affecting Response**

patients enrolled for the study the majority of them were males accounting for 27 of the total. The age of the patients ranged from 24 to 69 years. The median age of the patients enrolled in the study was 50 years.

The patients had an almost equal representation of the AJCC stage grouping with 16 patients in the Stage III (53.28%) and 14 patients in the Stage IV (46.62%) (figure-1).

The TNM staging of the patients showed majority of the patients being in the T4 stage (n=16, 53.28%) and the N staging most commonly seen was N2 (n=18, 59.94%).

Majority of the study population had histology which was moderately differentiated accounting for 63.27% (n=19 patients).

All the patients enrolled in the study received 3 cycles of Paclitaxel, Cisplatin and 5 FU with all the necessary precautions and pre-medication. The significant hematological toxicities encountered during the induction phase were graded with RTOG grading and CTCAE V.4.

Radiotherapy was delivered in conventional fractionation of 2 Gy per day over 5 days a week to a total dose of 66 – 70 Gy. The toxicities encountered during radiotherapy were graded using RTOG acute morbidity scoring criteria (figure-2).

All the patients had a clinically evaluable response after the induction chemotherapy. 9 of the 30 patients had a complete response at both the primary and nodal site (29.97%). Subset analysis shows that 6/19 moderately differentiated and 3/7 poorly differentiated cancers achieved a complete response following induction chemotherapy. N3 nodes had a very good response rates with 5 out the 7 patients achieving complete response. The hypopharyngeal cancers had the maximum benefit from the chemotherapy (n=4). Following the completion of the entire treatment schedule of induction chemotherapy and the concurrent chemoradiation, the response rates were evaluated. There was complete response at the primary site in 19 (63.27%) and complete response at the nodal sites in 24 patients (79.92%). The overall complete response rate at both the primary and the secondary nodal sites together was 19 (63.27%).



**Site and Response:** With regard to the site of involvement, nearly half of the oral cavity patients had only a partial response, 4 out of the 9 patients. In the case of oropharynx and hypopharynx, the response rates were near complete. 6 out of the 7 oropharynx cases and 8 out of the 9 hypopharyngeal cancers achieved complete response. The oropharyngeal and hypopharyngeal malignancies significantly fared better compared to the buccal mucosa and laryngeal cases ( $p=0.015$ ) (figure-4).

T1 and T2 had 100% complete response rates and there was one failure in T3 disease. It was in the T4 group the results were poor. There was complete response in 6 out of the 14 patients (42.8%). 5 out of 7 N3 node patients had a complete response, a success rate of 71.42% ( $p=0.6$ ). When comparing the response rates between T3 and T4, there was no statistically significant difference between them ( $p=0.18$ ). But when comparison was done between T1 and T2 taken together with T3 and T4 taken together, there was significantly better response in the earlier group ( $p=0.01$ ) (table-1).

**Stage and Response:** When analyzed with regard to the stage grouping, Stage III patient had complete response in 13 of the 16 patients who underwent complete treatment. Whereas in stage IV, only 50% had a complete response, of the total of 12 patients who completed the intended treatment. However this difference in the response was not significant. ( $p=0.09$ )

#### Histology

The complete response rate was very good in the case of poorly differentiated cancers with 85.71% (6/7). Also, in moderately differentiated cancers too, the response rates were good with 12 out of the total 17 achieving CR. However, there was no statistical difference between the response rates of the moderately and poorly differentiated tumors ( $p=0.4$ ). Whereas, all the well-differentiated cancers had a partial response. ( $p=0.01$ )

#### Delay in RT

Those who had a delay in the completion of the course of radiotherapy, more than half of them had a partial response (5 out of 9, 55.56%) ( $p=0.08$ ). In other words, in those achieving a complete response only 4 out of the total 19 had a delay in RT (21.05%).

### DISCUSSION

The results of the present study show that sequential therapy is feasible in our setup and should be considered in select cases of locally advanced head and neck cancers.

The study included a wide range of patients across the age groups between the eligibility ages of 18 years to 70 years. The study population was heavily dominated by males with only 3 females. But this was probably due to higher exposure to carcinogens as males are more commonly users of cigarettes, beedis and the other smokeless tobacco forms like pan, khaini etc.

All the patients started on the protocol completed the entire course of three cycles of the induction chemotherapy. This compliance for induction phase of the trial is similar to

other trials in the available literature. But two patients did not proceed onto radiotherapy following the completion of induction phase. The probable reason for these patients defaulting was due to the alleviation of symptoms or due to the adverse effects of chemotherapy. This implies indirectly that it is important to select cases carefully for this regimen. Patients with good nutritional status at the start of the treatment are perhaps better suited to undergo the rigors of this intense treatment regimen better. The patients should be counseled clearly before the start of the treatment that radiotherapy is the essential part of treatment and has to be delivered at the right time after induction chemotherapy or else the benefits of chemotherapy will be lost. Probably literacy will play a major role in this regard with literate people being able to grasp the consequences of defaulting radiotherapy. Economic factors also have to be taken into account in our country as this prolonged treatment process may take a heavy toll on the family. Most commonly the patient, a male, turns out to be the sole breadwinner of the family and if he is repeatedly in hospital for the course of the treatment then the financial burden on the family becomes manifold and this prompts the patient to default treatment.<sup>11</sup> In the TAX 324 study, almost all the patients completed the entire induction phase in the TPF arm (98%). But only 79% of the patients in TPF arm proceeded to receive the chemoradiotherapy. In the TAX 323 study, nearly 25% discontinued the chemotherapy. But the most common reason quoted by the authors for discontinuation is progressive disease. In the present study, there were no cases of disease progression during the treatment course.<sup>12</sup>

There were 2 cases of grade 4/ febrile neutropenia cases recorded in the trial. But there were no deaths recorded during the trial. Febrile neutropenia was 5.2% in the Tax 323 study and 4.8% in the Tax 324 study. Similar to TAX studies the grade 3 and grade 4 neutropenia were more common. The TAX studies too did not allow primary prophylaxis with G-CSF which probably resulted in a high incidence of grade 3 and grade 4 neutropenia in those studies. So, appropriate modifications were done in the study protocol. The present study also denied primary prophylaxis with G-CSF during the first cycle of induction chemotherapy. But if they needed G-CSF before the start of the subsequent cycle of induction chemotherapy, they were given primary prophylaxis with G-CSF during the subsequent cycles. Thus there was no undue delay in the subsequent cycles of chemotherapy due to hematological toxicities. And also all the patients received the entire planned 3 cycles.<sup>12</sup>

Paclitaxel did not result in any untoward allergic reactions in any of the patient but all patients were put on steroids as a precautionary measure. The induction regimen also included a highly emetogenic drug like Cisplatin. This resulted in grade 3 nausea in 4 patients which needed IV fluid administration. The TAX studies recorded grade 3 or grade 4 nausea in around 5% of the patients.<sup>12</sup> The present recorded a 13.32% grade 3 nausea but no cases of grade 4 nausea. The nausea was appropriately managed with IV fluids to correct dehydration and with antiemetic like metoclopramide and

dexamethasone. The Tax 323 study had a grade 3 or grade 4 diarrhea in 5 out of 177 patients (2.8%) and in TAX 324 study, 7 out of 251 patients (2.8%). The present study also had a similar rate of grade 3 or 4 reactions (6.67%). These patients were appropriately managed. They were advised by plenty of fluid intake of 2-3L per day. IV fluids were administered in the case of severe dehydration which was not corrected by oral rehydration alone. Antispasmodics and anti-motility agents were used to reduce the frequency and to manage the abdominal cramps and pain. Regular monitoring of the biochemical parameters like serum electrolytes and renal function tests were done.<sup>12</sup>

The study revealed the advantages of induction chemotherapy followed by concurrent chemoradiation in locally advanced head and neck cancers. There was 30% complete response (CR) rate following the completion of the induction phase. This was similar to the 17% and 8.5% complete response rates seen in the TAX studies following induction TPF chemotherapy which was significantly higher than the comparative arm of PF induction therapy. This advantage was more in the case of N3 nodes with most responding by the end of the induction phase. Probably N3 nodes would benefit the most from the sequential chemoradiation. Also the subsites of hypopharynx and oropharynx had the best response to the entire treatment protocol. And this was significant when compared to the response rates of the other subsites of oral cavity and the larynx ( $p=0.015$ ). This probably points to the role of induction chemotherapy in organ-preserving therapy. The toxicities encountered during radiotherapy and concurrent chemotherapy did not vary much from the regular upfront radiotherapy patients. Most of them received at least 4 cycles of the planned 6 cycles of weekly chemotherapy.<sup>12</sup>

Unlike the TAX 323 study which delivered 4 different schedules of radiotherapy and similar to the TAX 324, radiation was delivered in conventional fashion of 2 Gy per fraction 5 days a week up to a total dose of 66 Gy. Since the non-inferiority of carboplatin to Cisplatin has not been proven beyond doubt in the concurrent setting, the present study delivered only Cisplatin as the concurrent chemotherapy.<sup>12,13</sup> The toxicity encountered during radiotherapy was stomatitis due to oral mucositis, dysphagia due to pharyngitis and esophagitis, dermatitis and dryness of mouth due to salivary gland toxicity (figure-3). Three patients (~10%) had grade 3 mucositis which warranted suspension of radiation and intervention with steroids and mouthwash as discussed earlier in the results section. This was similar to the rates of stomatitis encountered in the TAX studies of 8.5% and 4.6% stomatitis. There were five cases of grade 3 reactions of dysphagia which required IV fluids and NG tube feeding (17.9%). The parent study recorded a grade 3 dysphagia rate of 5.2%.<sup>12</sup>

Both stomatitis and dysphagia are very important as they have serious implications regarding the time duration of treatment. It is a well-known fact that even a delay of single day in completing the radiotherapy will have a considerable reduction in local control and disease-free survival. So

precautions were taken to prevent the development of grade 3 toxicities by instituting steroids and regular mouthwash with soda bicarb solutions and antibacterial solutions as described in the methodology of the protocol.<sup>13</sup>

All these toxicities resulted in treatment breaks during radiotherapy in 9 patients out of the twenty-eight who had undergone chemoradiation. (30%).

The overall complete response rates at the end of the entire schedule of the treatment was 63.27% ( $n=19$ ). The TAX 323 study had recorded 72% complete response rates among those who were started on the chemoradiation schedule.<sup>12</sup>

When analyzed with regard to site of involvement, the oral cavity patients had a very poor response to this regimen. Whereas the hypopharyngeal and oropharyngeal cancers had a near total complete response rate of 88.89% and 85.71% respectively. This better response in these two subsites of the head and neck proved to be statistically significant ( $p=0.015$ ). Differentiation which is probably a surrogate for the mitotic rate of the tumor cells showed a significant correlation with response rates with all 4 well-differentiated cancers resulting in partial responses ( $p=0.01$ ). Most of them were buccal mucosa cancers. This implies that sequential therapy is not the best approach for buccal mucosa as most of the buccal mucosa cancers will be of well-differentiated histology. But the poorly differentiated tumors and moderately differentiated tumors had a very good complete response rate of 85.71% and 70.6% respectively. ( $p=0.4$ ).

It has already been deduced that oropharyngeal and hypopharyngeal cancers had a good response rate. This is probably due to the fact these sites will have more of moderate and poorly differentiated tumors. So, probably these are the two subsites which will have the best response in a sequential therapy setting. But the other factors such as stage and nutritional status of the patient will also have an implication on the treatment outcome.

It is a known fact that the T size of the primary will have an impact on the immediate locoregional control as well as the recurrence-free survival. The present study has confirmed the same fact with T1-T3 tumors achieving more complete responses. The lesser T stages T1 and T2 had a significantly better response rate when compared to the T3 and T4 stages ( $p=0.01$ ). But this difference was not evident between the stages T3 and T4 ( $p=0.18$ ). Also the N3 node status had a very good response to this sequence with 5 out of 7 resolving completely (71.42%). But this better response rate in the patients with N3 nodes was not statistically significant ( $p=0.6$ ). The prognostic significance of stage grouping is that involvement of nodes which upgrades the stage grouping to stage III reduces the survival by 50%. In the present study also stage III patients had a better response than the stage IV patients.

As already seen it is a known fact that even a single day of delay in the radiotherapy schedule is detrimental to the final outcome. More than half of those who had a delay in RT had partial responses as the outcome and this was statistically significant ( $p=0.08$ ). In contrast in those who had a complete response only 21% had treatment breaks.

## CONCLUSION

In conclusion, head and neck cancers continue to be a public health problem afflicting the developing countries. And most of these patients are still presenting in the advanced stages. So, studies like the present one examining intensification of the treatment regimen to achieve better results needs to be carried out.

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